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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-16, 21-27, 37, and 39-50 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 17-20, 28-36, and 38 have been cancelled.
3. ☑ Claims 21-27 and 44-47 are allowed.
4. ☑ Claims 1-13, 15, 16, 37, 39-43, and 48-50 are rejected.
5. ☑ Claims 14 are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

Miscellaneous

1. The following is a supplemental action to the Office action mailed 23 November 1994. Accordingly, the period for response has been reset.

2. The terminal Disclaimer, filed 19 January 1993, is proper and has been recorded. Accordingly, the obviousness-type double patenting rejection has been withdrawn.

3. In the Office action of December 13, 1993 (Paper No. 11), claims 35, 36, and 38 were rejected under 35 USC 112, first paragraph, and claims 17-20 were rejected under 35 USC 103. The amendment received December 27, 1993 (Paper No. 12; Amendment D) cancelled claims 17-20, 28-36, and 38. Accordingly, the rejections of claims 35, 36, and 38 under 35 USC 112, first paragraph, and the rejection of claims 17-20 under 35 USC 103 were withdrawn as the cancellation of said claims rendered the rejection of same moot. Claims 28-34 were drawn to a non-elected invention as a result of the restriction requirement found in the Office action of March 25, 1993.

4. In the Office action of January 13, 1994 (Paper No. 14) a new ground of rejection under 35 USC 112, first paragraph, was applied against claims 1-16 (new matter), and claims 1-13, 15, 16, 37, and 39-41 (enablement). A new ground of rejection was also made under 35 USC 112, second paragraph, against claims 1-16, 26, 27, 37, and 39-43. In the Office action of November 23, 1994 (Paper No. 18), claims 21-27, 37, and 39-43 were indicated as being

allowable; and a rejection was made under 35 USC 112, first paragraph, as it relates to claims 1-13, 15,and 16 (enablement), and claim 14 (scope).

5. In the response received 18 July 1994, Paper No. 16, Amendment E, a request for the entry of claims 17-20, 35, 36, and 38 was made. The Office action of 23 November 1994 indicated that this portion of the amendment had not been entered. Upon review of the record, it is noted that claims 17-20, 35, 36, and 38 had each been cancelled; see page 1 of the amendment received 27 December 1993, Paper No. 12, Amendment D. However, since the prior Office action was not made final, the entry of the claims is in order. Therefore, "new" claims 17-20, 35, 36, and 38 have ben entered. Note, however, that they have been renumbered as provided under 37 C.F.R. 1.126 such that they now appear as claims 44-50. Claims 45 and 46 have had their dependency renumbered to that of claim 44.

Re. Declarations

The declaration of Peter Greshoff, received 23 September 1992, Paper No. 2. 1/2 has been fully considered with the following effect:

The crucial correlation between different soybean cultivars is discussed with intermediate results (microheterogeneity data conclusions) without any actual data for evaluation of this crucial element. A conclusion regarding specific soybean is presented which is then generalized in an opinion that this supported a broad scope of enablement regarding loci for which the invention is applicable. There is an absence of even the simplest correlative data. Such absence of correlative data renders the declaration very weak as it is therefore based primarily on opinion.

Therefore, in the absence of convincing evidence to the contrary, the declaration has not been found to be persuasive of the claims being entitled to a broad scope.

The declaration of Leroy Hood, received 28 September 1993, Paper No. 9, has been fully considered with the following effect:

It is apparent that Dr. Hood sequenced a "single" 100K base region in mouse and man and compared sequences. This comparison does not compare alleles in a multiallele locus but rather compares a single allele in mouse with a single allele in man. Dr. Hood admits that man and mouse diverged millions of years ago and concludes that the 70% homology over the non-coding region (95% of the compared sequence) under evolutionary pressure is striking and conclusive regarding the correlation between alleles and nearby non-coding regions. This conclusion is based on assuming that the divergence of mouse and man in evolution as to species is the same phenomenon as that which causes multiallelic variation. This assumption is never discussed and is not supported. Additionally. the 70% homology between man and mouse may be viewed equally well as 30% non-homology wherein random mutations cause this non-homology without any "correlative" mutations between coding and non-coding regions. That is, do mutations in coding regions follow or correlate to mutations in the non-coding region? No answer is given in this declaration to this critical question. Also, since only 5% of the 10K region sequenced by Dr. Hood is coding region, the crucial sequence homology data between coding regions is deeply hidden in the data. That is, maybe the coding regions have 90%, or maybe 20%, homology between man and mouse whereas the non-coding regions have a little less

or more than 70% homology, respectively, so that 70% overall homology of the region is obtained. In fact, Dr. Hood's statement of the T-cell receptor genes as the paradigm of diversity suggests that these genes may have near 0% homology to any other region or species and are likely to be very multiallelic. Such divergence would indicate that the scope of the instant invention lacks enablement when attempting to correlate coding and non-coding regions. This determinative data was not supplied. Dr. Hood's declaration is based upon a lack of the critical data: specially lacking are any comparisons between alleles but rather only species comparisons. It would appear, however, that the instant invention is not directed to interspecies comparisons. The attempt to use broad evolutionary reasoning to support his conclusion is not found persuasive as it appears distant to the limited practice of the instant invention. Accordingly, the declaration is not found persuasive.

The declaration of Dr. Pablo Rubinstein, received 08 August 1994, Paper No. 17, has been fully considered with the following effect:

This review of published articles appears to be the most persuasive declaration of the three regarding the generic nature of the correlation of non-coding and coding regions but this declaration is limited to correlating "intron" variation to "exon" variation and has other concerns discussed below. As for evidence in support of the instant invention, the scope of the declaration is found to only cover intron-exon correlation and does not pertain to any or all non-coding region variation that is "nearby" to a coding region. Analysis of the four references in this Declaration is given as follows:

a) Eisses et al. - This article teaches the sequencing of three *Drosophila* Adh alleles and finds differences in each of the three related introns. There is, however, no evidence that the differences in the alleles is correlated to differences in the introns. That is, not one duplicate allele in another sample was sequences regarding an intron to show that intron variation is correlated to coding region variation. Therefore, there is no convincing evidence that allele identification is possible via intron sequencing.

b) Messer et al. - This article does provide good evidence of a TNF-β allele that is correlated to an intron polymorphism. However, the evidence is presented in an article that was published subsequent to the filing date of the application. Accordingly, it does not substantiate the level of skill in the art at the time the invention was made nor does it present evidence that one of skill in the art at the time the invention was made would have been able to or even aware that the TNF-β allele could be correlated to an intronic polymorphism.

c) Brooks et al. - This is another good reference for the correlation of the instant invention regarding the aldolase gene. However, this article was published three years after the most recent filing date. It, like that of Messer et al., does not support the enablement of the claimed invention at the time the invention was made less one engage in hindsight reconstruction for there is no evidence in the record which suggests that one of skill in the art at the time the invention was made would be interested in or even contemplate an association of a widespread A149P hereditary fructose intolerance mutation with sequence polymorphisms in the aldolase B gene when the sequence polymorphisms are in themselves described as being "newly identified".

d) Schlieben et al. - This article provides an analysis of polymorphisms. It is seen that all of the allele correlated mutations are in the exon that is analyzed. One of the primers used for PCR amplification in this article is directed to an intron but none of the intron sequences are correlated to allelic variation.

In summary, none of the above references provide good evidence in support of the Declaration's conclusion. Accordingly, this Declaration, along with the other two declarations, are deemed non-persuasive to prevent or overcome a scope rejection directed against the instant invention based on a lack of enablement beyond HLA locus usage.

Rejection under 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15, 16, 37, 39-43, and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the method of claims 21-27, 44-47, and claim 14.

The specification does not set forth a repeatable procedure whereby one of skill in the art at the time the invention was made would be able to effectively determine where such relationships exist between exons and introns. Further, the specification does not enable one of skill in the art at the time the invention was made to perform such amplification reactions where

the size of the nucleic acid to be amplified can be of virtually any length. Attention is again directed to the publication of Padgett et al., (p. 1124, second par.) where it states that "The length of introns in vertebrate genes ranges from approximately 50 to well over 10,000 bases with no obvious periodicity." While this publication only makes reference to that encountered in vertebrates, the claimed method has sufficient breadth of scope so to encompass not only all vertebrates but invertebrates, plants and fungi as well. Special attention is directed to applicant's interpretation of the term "intron". While the intervening, non-coding, sequences found between exons of a given gene are accepted in the art as being equated with an "intron", applicant has broadened this meaning to also include "5' and 3' untranslated regions associated with a genetic locus. In addition the term is used to refer to the spacing sequences between genetic loci (intergenic spacing sequences) which are not associated with a coding region..." (specification at p. 10, ll. 29-35). Clearly such a broad definition of "intron" allows for the interpretation of the claims to encompass the amplification of extremely large sequences whose size cannot be readily predicted and accordingly, sequences which cannot be amplified because of their immense size. Even if the claims were limited to the art-accepted meaning of "intron", such would encompass sequences of sizes far greater than one could reasonably expect to be amplified. In support of this holding, attention is directed to the publication of Allen et al. There it is seen that PCR was used to amplify polymorphisms. At page 736, center column, it is seen that amplification of a target nucleic acid was carried out only up to 400 bp, however, the functional limitation appeared to be at 2500 bp (p. 737, center col., third par.). Clearly, the aspect of amplifying a sequence of 2500 bp is far less than the size of many introns, which as shown above

exceed 10,000 bp. Therefore, one would not be able to amplify the intronic sequences and exon(s) which are targeted. The specification has not provided guidance as to how these limitations can be overcome. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Rejection under 35 U.S.C. 112, second paragraph

Claims 2, 6, and 50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite with respect to the sue of the phrase "at least about 300 nucleotides." The term "about" encompasses values above and blow the identified point. Yet, the phrase "at least" is in contradiction to

Claim 50 is indefinite a result of the phrase "not more than about one kilobase". The term "about" encompasses values above and below the indicated point. Therefore, the scope of "about" is in contradiction to the phrase "not more than". Accordingly, one is not able to determine the metes and bounds of the claim.

Rejection under 35 U.S.C. 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-11 are rejected under 35 U.S.C. § 103 as being unpatentable over Wai Kan et al., in view of Mullis.

Wai Kan et al., (p. 5631, left col., second par.) taches the identification of genetic polymorphisms at a restriction site which is close to the human β-globin structural gene. In the last sentence of said par., it is stated: "This type of polymorphism may be useful for linkage analysis, parental diagnosis, or anthropological studies." In the abstract, it is taught that this polymorphism is located "about 5000 nucleotides from the 3' end of the β-globin structural gene."

Wai Kan et al., do not teach amplification of the nucleic acid sequence.

Mullis et al., each performing polymerase chain reaction (PCR) amplification of a target nucleic acid. The nucleic acid or acids may be obtained from any source, including bacteria, yeast, viruses, and higher organisms such as plants or animals (col. 7, l. 66, bridging to col. 8., l. 2). PCR can be used to amplify a gene of interest, e.g., human beta-hemoglobin or the human HLA DQ, DR or DP-α and -β genes (col. 16, ll. 25-28). PCR may also be used to enable detection and/or characterization of specific nucleic acid sequences associated with infectious diseases, genetic disorders or cellular disorders such as cancer... Amplification is useful when the amount of nucleic acid available for analysis is very small, as, for example, in the parental

diagnosis of sickle cell anemia using DNA obtained from fetal cells..." (col. 18, third par.). Genetic diseases is defined as including "specific deletions and/or mutations in genomic DNA from any organism, such as e.g., sickle cell anemia, cystic fibrosis, α-thalassemia, β -thalassemia,and the like" (col. 18, fourth par.).

In view of the showing of the prior art of record, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the method of PCR amplification as taught by Mullis et al., with the method of Wai Kan et al., such that one could amplify the polymorphism of DNA sequence adjacent to human β-globin structural gene and thereby be better able to detect and study this relationship to sickle mutation. One of ordinary skill in the art at the time would be motivated to combine these methodologies as PCR allows for the amplification of minute quantities of nucleic acid as well as increasing the number of copies of a target nucleic acid to such a level whereby it may be more readily detected. This of particular importance as the sequence being detected by Wai Kan et al., is found in genomic DNA which has low copy number of the target sequence. Therefore, in order to better detect and study this polymorphism, amplification of the target sequence would be an obvious application of currently available technology.

Remarks

Claim 14 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on Monday through Thursday from 6:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Moskowitz Parr, can be reached on (703) 308-2454. The fax phone number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. Parr 4/25/95

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25 April 1995